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APPELLANTS' REPLY BRIEF Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	RICE-012
	Confirmation No.	8868
	First Named Inventor	DALY, ROGER J.
	Application Number	09/509,196
	Filing Date	March 23, 2000
	Group Art Unit	1649
	Examiner Name	CHERNYSHEV, O.
	Title: "A POTENTIAL EFFECTOR FOR THE GRB7 FAMILY OF SIGNALLING PROTEINS"	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on September 18, 2006.

By virtue of the fact that in the Examiner's Answer the Examiner (1) changed the statement and grounds of rejection for the rejection of Claims 5-7, 19-22, 24-29, and 31-41 under 35 U.S.C. § 101 from those used in the Final Rejection and (2) reintroduced issues in the Examiner's Answer which were not clearly used as basis for the Final Rejection, Appellants respectfully request that this application be remanded to the Examiner for the issuance of a second Examiner's Answer including a New Ground of Rejection.

The Commissioner is hereby authorized to charge deposit account number 50-0815 to cover any fee required under 37 C.F.R. §1.17(c) for filing Appellants' reply brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815.

REPLY BRIEF and REQUEST FOR REMAND

In this Reply Brief, Appellants address comments made in the Examiner's Answer mailed September 18, 2006. By changing the statement of rejection and by reintroducing issues used in the explanation of the rejection, the Examiner has raised new grounds of rejection in the Examiner's Answer. The Appellants note that all arguments presented in the prior Appeal Brief still apply with equal force, but are not reiterated in full herein solely in the interest of brevity and for the convenience of the Board.

Under section (9) Grounds of Rejection of the Examiner's Answer, the Examiner stated the grounds for the rejection of Claims 5-7, 19-22, 24-29, and 31-41 under 35 U.S.C. § 101 as "the claimed invention is not supported by either a specific and substantial credible asserted utility or a well-established utility." Answer at page 3 (emphasis added). **The facet of the rejection based on the alleged absence of a well-established utility was not present in the Final Rejection, and appeared for the first time in the Examiner's Answer.**

The Examiner reintroduced additional issues in the Examiner's Answer. For example, the Examiner raised the orphan protein issue at page 3 and the issue of a candidate effector protein of yet undetermined function or biological significance at pages 4 and 5. These issues first appeared in a non-final Office action mailed April 2, 2001. However, these issues were not used specifically as basis for the Final Rejection. Rather, the Examiner made the Final Rejection "*essentially* for reasons of record in appropriate sections of previous office actions of record." Answer at page 2 (emphasis added).

Accordingly, the actual specific basis for the outstanding final rejection under 35 U.S.C. § 101 was not made clear to Appellants until the Examiner's Answer when the basis for rejection was set forth specifically. The Final Rejection did not state that the above issues formed the basis for the rejection. As such, these issues were not addressed in Appellants' Brief on Appeal.

Appellants will respond first to the specific issues reintroduced in the Examiner's Answer:

Issues Reintroduced in the Examiner's Answer

1. The Examiner has concluded that the subject protein encoded by the claimed polynucleotide is an orphan protein.

Although the Examiner has not defined her use of the term *orphan protein*, Appellants presume that the Examiner is of the opinion that no function has been established for the protein even though the protein has been sequenced.

The polynucleotide of the present invention has been identified using a yeast two hybrid screen on the basis of its encoding a polypeptide that specifically binds to full length Grb14, a member of the Grb7 family (see, e.g., specification page 6, line 12 to page 9, line 23). This fact establishes immediate *functional information* about Appellants' polypeptide, i.e., the polypeptide interacts with Grb14. This information is disclosed in Appellants' specification as filed.

Furthermore, Appellants disclosed in their specification that the 2.2412 protein encoded by the claimed polynucleotides binds to Grb7 as well as to Grb14 using a GST pull down assay, and described that the 2.2412 N-terminus bound more strongly than the C-terminus (specification page 10, line 26 to page 11, line 10). Since these data were generated using a GST pull down assay, these results further confirmed those of the yeast two-hybrid assay discussed above. In addition, Appellants have mapped the genomic position of the newly identified sequence (page 10, lines 11 to 24), and have mapped the region of Grb14 to which the protein encoded by the claimed polynucleotides binds (page 11, lines 12 to 32). This work represents a significant amount of actual biochemical characterization which would provide structural information to the person skilled in the art.

Before the priority data of the present application, the Grb7 family of SH2 domain-containing proteins had been shown to be associated with esophageal carcinoma (Tanaka et al. 1997, Cancer Research 57: 28-31); primary gastric cancer (Kishi et al. 1997, Biochem Biophys Res Commun 232(2): 5-9); and breast cancer (Stein et al. 1994, EMBO J 13(6): 1331-40). Furthermore, the Grb7 family of proteins includes not only a motif characteristic of a protein involved in a signal pathway (an SH2 domain), but also a domain shared with a protein termed Mig10, which is involved in neuronal cell migration (Daly et al. 1996, J Biol Chem 272:

12502-12510). SH2 domain-containing proteins were known to interact with tyrosine kinase receptors, which in turn are known to play a role in both cell cycle regulation and cell migration.

In addition, Grb7 had been shown to bind to Human EGF receptor 2, known to play an important role in a number of tumors, including breast cancer (Stein et al. 1994). In the same report, Grb7 was shown to bind to tyrosine phosphorylated SHC. Subsequent reports showed that Grb7 regulates cell migration positively (Tanaka et al. 1998, J Clin Invest 102: 821-827; Han et al. 1999, J Biol Chem 274: 24425-24430; and Tanaka et al. 2000, J Clin Invest 183: 411-415) and that this is likely to increase the invasion or metastasis of cancer cells.

These findings provide very strong evidence that the Grb7 family proteins are signal transduction molecules the aberrant expression of which is associated with human tumors. The identification of cellular proteins which interact with SH2 domain proteins involved in cell signaling is important because these other cellular proteins are highly likely to be regulators or effectors of the function of the SH2 domain proteins. Consequently, the identification of a protein that binds to the Grb7 family of proteins, including Grb7 and Grb14, is an important finding.

Given the knowledge in the art and the data disclosed in the specification, the conclusions drawn in the specification are that the protein encoded by clone 2.2412 represents a general effector of the Grb7 family (page 11, lines 9 and 10; page 11, lines 29 to 32). Given the fact (see above) that the Grb7 family had already been characterized before the priority date of the present application, the identification of a protein which binds to the Grb7 family would present the person skilled in the art with an immediate and apparent function and utility for such a protein.

Therefore, the Examiner is mistaken that the subject protein encoded by the claimed polynucleotide is an orphan protein.

2. The Examiner has concluded that designating the polypeptide encoded by the claimed polynucleotides as a candidate effector protein (with a yet undetermined function or biological significance) for Grb7 proteins does not make the instant DNA or encoded protein diagnostic of cancer.

Appellants have established in the file record that it was known in the art as of Appellants' filing date that Grb7 and Grb14 are differentially expressed in cancer cells (breast, prostate, gastric, and esophageal cancer) compared to normal cells. Appellants have provided extrinsic evidence that Grb7 and Grb14 were recognized as markers for cancer at the time of filing of the present application, as well as extrinsic and intrinsic evidence[1] that the 2.2412 polypeptide encoded by the claimed polynucleotide specifically binds to Grb7 and Grb14 (see, e.g., specification page 10, line 26 to page 11, line 10) Appellants asserted at page 5 of the specification that detection of the protein encoded by the cDNA 2.2412 in a sample should provide a useful tumor marker and/or prognostic indicator for these cancers.

However, the Examiner is requiring data showing altered levels or forms of a polynucleotide encoding 2.2412 polypeptide in diseased tissue versus corresponding healthy tissue. Answer at pages 5 to 6 and 8. In addition, the Examiner asserted that further research would be necessary to discover the association of 2.2412 protein with particular cancers. In essence, the Examiner is requiring that Appellants prove their utility statements unequivocally. As pointed out in Appellants' brief, such a requirement amounts to application of a standard higher than the preponderance of the evidence standard used in utility rejections. In fact, Appellants are not required to prove their utility unequivocally.[2]

Further, the Examiner is improperly requiring that such data be present in the application as filed originally. See Final Rejection, page 4, first paragraph; Answer at page 5, lines 5 to 8 ("[t]he instant specification fails to provide any evidence or sound scientific reasoning to allow a conclusion that the instant 2.2412 protein encoded by the claimed polynucleotides is associated with any type of cancer, including prostate or breast cancer"). As Appellants pointed out in their brief, extrinsic evidence in

[1] See the specification at, for example, pages 10-11.
[2] The Examiner also applied this improper standard at page 12, line 14 of the Answer.

support of a utility statement, as opposed to the utility statement itself, need not be recited in the application as filed.

Contrary to the Examiner's position, Appellants have established such an association. Contrary to the Examiner's position, Appellants' assertion of tumor marker utility is a patentable utility that would be apparent immediately to the skilled artisan, who would have knowledge of the extrinsic evidence of record. However, the Examiner's positions are based on her refusal to consider the extrinsic evidence of record.

The Examiner has looked only to the specification and then misquoted it at page 6, lines 13 and 14 of the Answer in order to reach an erroneous conclusion "that the novel polypeptide 2.2412 cannot possibly be a specific marker for any cancer cells due to the [sic] its presence in 'all cells.'" Answer at page 6. The Examiner reached this conclusion from her misquotation from page 10, second paragraph of the specification which properly reads, "[t]his resulted in the detection of a single mRNA transcript of approximately 7 kb in all tissues examined with the exception of the kidney. "(Emphasis added).

Respectfully, this statement represents a misunderstanding of how cancer markers are useful. A gene product need not be expressed ONLY in cancer cells and not in normal cells, as the Examiner's statement seems to imply. Instead, cancer markers are useful if they are expressed at *different* levels in cancerous cells as compared to non-cancerous cells. The fact that 2.2412 is expressed in normal cells, then, does not *a priori* mean 2.2412 can not be used to detect cancerous cells. Moreover, Appellants have provided data to demonstrate the assertion that 2.2412 is differentially expressed in cancerous cells (see Declaration of Yasumichi Hitoshi under 37 C.F.R. §1.132, submitted February 4, 2003 (the "Hitoshi declaration")).

Appellants' assertion in the specification, viewed in light of the extrinsic evidence of record and in light of the knowledge of the skilled artisan, is sufficient to satisfy the requirements under §101.

Response to Arguments in Examiner's Answer

Appellants will now address various arguments set forth in the Examiner's Answer:

1. The Examiner argued at page 10 that there is no evidence of record that 2.2412 binds exclusively to Grb7 or Grb14 proteins. Once again the Examiner is asking improperly for unequivocal proof of utility.

2. The Examiner concluded based on the alleged absence of evidence of record that 2.2412 binds exclusively to Grb7 or Grb14 proteins that "it is not clear and is not explained in the instant specification as filed as [sic] how 2.2412 could be used as a cancer marker based on its binding ability." Answer at page 10 (emphasis added).

The above quotation is inconsistent with the Examiner's assertion that no evidence was dismissed and all publications submitted by Appellants were considered (Answer at page 13). As pointed out above, Appellants' assertion of tumor marker utility is a patentable utility that would be apparent immediately to the skilled artisan, who would have knowledge of the extrinsic evidence of record, without further explanation in the specification.

3. The Examiner asserted at page 12 that the articles by Kishi et al. and Tanaka et al. relate to coexpression and coamplification of Grb7 in gastric and esophageal cancers, respectively, but the specification as filed does not assert a specific utility with respect to these cancers.

As pointed out in their brief, Appellants have disclosed[3] that the Grb7 family proteins exhibit differential expression in certain human cancers (particularly breast and prostate cancer) (emphasis added). The phrase *certain human cancers* is a generic statement that embraces the gastric and esophageal cancers disclosed by the Kishi *et al.* and Tanaka *et al.* articles, respectively, cited by Appellants in support of their utility statement. Breast and prostate cancers are examples falling within the generic utility statement.

Apparently the Examiner is requiring that a generic statement of utility be accompanied by an exhaustive litany of specific utilities that fall within the generic utility statement in order for earlier or later published specific knowledge to

[3] See the specification at, for example, page 5.

substantiate Appellants' assertion of utility. This is an unduly burdensome and improper standard tantamount to the Examiner's unequivocal proof of utility.

4. The Examiner criticized the Hitoshi declaration for its "limited data." Answer at page 14. Once again, the Examiner is improperly requiring unequivocal proof of specific utility.

The Hitoshi declaration contains additional data that confirms the use of the 2.2412 protein as a tumor marker. Dr. Hitoshi declared that at least two publications have associated 2.2412 expression with human cancers. Specifically, 2.2412 has been reported to be a tumor-specific antigen as evidenced by detection of 2.2412 antibodies in sera of breast cancer patients[4] and in sera of patients having meningioma.[5]

Furthermore, Dr. Hitoshi declared that it in his opinion a person having ordinary skill in the art reading the instant application at the time of the filing thereof would have found the assertion that 2.2412 is a tumor marker to be credible. This alone should be sufficient to establish utility, but Dr. Hitoshi declared further that the additional data submitted in the declaration further support the assertion in the instant application that the 2.2412 protein and its encoding polynucleotide are useful as a tumor marker.

5. The Examiner asserted that as in *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005), Appellants' asserted utility is "so vague as to be meaningless." Answer at page 16. This is a gross overstatement based on the Examiner's view that the specification states that 2.2412 is "ubiquitously expressed in almost all tissues," which is based on a misquotation of Appellants' specification. See above. In addition, the Examiner's conclusion would require that a gene product could only be useful in detection of cancerous cells if it is expressed *only* in cancerous cells and not in normal cells. This is not correct, as discussed above. In short, the Examiner's statement bears no relationship to the facts and evidence in the application.

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[4] Kuimov et al., 2001 Genes Immun. 2:52-5.
[5] Monz et al., 2001 Clin. Cancer Res. 7:113-9.

6. With respect to the procedural flaws in the § 101 rejection, as set forth in Appellants' brief, the Examiner has presented no reason why MPEP § 2107 II(B) should control MPEP § 2107 II(C) or the Utility Guidelines. Therefore, the actual statement of the rejection remains flawed owing to the presence of the word *credible* therein.

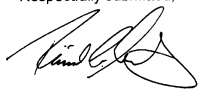
With respect to Appellants request for issuance of a second Examiner's Answer, Appellants note that while the new statement of rejection under § 101 refers to an unsupported well-established utility, the Examiner has not put forth in the Answer an explanation of lack of support for a well-established utility, as required by the Utility Guidelines. As such, the rejection is not only a new ground of rejection, it is also an unexplained new ground of rejection.

Therefore, Appellants submit that the facts and circumstances set forth above, as well as equity, call for the issuance of a second Examiner's Answer containing a new ground of rejection so that Appellants may respond fully and with all means available to them to the new grounds and issues raised in the Answer. Because a new ground of rejection was not made, Appellants are now unfairly precluded under 37 C.F.R. § 41.41(a)(2) from submitting any affidavit or other evidence.

SUMMARY

The Appellants respectfully request that the rejection of under 35 U.S.C. §§ 101 and 112, first paragraph be reversed, or in the alternative that the application be remanded to the Examiner with instructions to issue a second Examiner's Answer including a New Ground of Rejection.

Respectfully submitted,



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